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(54) Title: A COMPOSITION AND A METHOD FOR TISSUE AUGMENTATION

(57) Abstract

The present invention provides a biocompatible composition for tissue augmentation, comprising a pseudoplastic polymer carrier in an amount of 0.05-50 % (w/w) of the total composition; and one or more tissue augmenting substance(s). Furthermore, the invention comprises a method for tissue augmentation, comprising: injecting the above composition into a desired site of the human or animal body for augmenting the tissue at and around said site.

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A COMPOSITION AND A METHOD FOR TISSUE AUGMENTATION

BACKGROUND OF THE INVENTION

The present invention relates to a composition and a method for tissue augmentation.

Tissue augmentation is desirable for both therapeutical and cosmetical purposes. A therapeutical application is, for example, augmentation of tissues that need to be enlarged for proper function. Examples of such are the vocal cords, the oesophagus, various sphinters that have become weakened or have too thin tissue mass. Another set of examples are enlargement of the muscles of, for instance, the urether and rectum. In the field of cosmetic surgery tissue augmentation is applied to wrinkles and scars as well as to enlarge lips or fill out age related diminished fat deposits around the eyes as well as other applications. In the cosmetical field, plastic surgeons fill out, for example, eye wrinkles, by injecting tissue augmenting materials.

Materials used for augmentation of tissues are, for instance, the patients own fat cell cartilage or other suitable materials. Commercially available biologically degradable materials include collagen suspensions and crosslinked hyaluronic acid. Non degradable materials include silicone oil, silicone microparticles, Teflon® paste and other inert materials.

US patent 5 007 940 teaches the use of deformable, nonbiodegradable hydrogels with a lubricious surface. The patent concerns injecting of nonbiodegradeable material which appears by the finding of such material in the brain tissues. Thus any material injected into tissues has a risk of being carried away by the venous blood to central parts of the body. For individuals with a life expectancy of several years this is not likely to be accepted by regulatory authorities. Therefore, such materials are presently not widely used due to migration to critical tissues or long term negative reactions on the health like autoimmune diseases or cancer.

Homotransplantation of tissue is a cumbersome and painful procedure that has a too short action. The most frequently used material today is collagen suspension. However it is made from bovine collagen and can carry unwanted slow action viruses. Most negative is the fact that some patients develop a sensitivity towards the material or get stimulated enzymatic activity in the skin due to repeated foreign body reactions. Despite these drawbacks the products are still very popular. An interesting new product under clinical evaluation is a crosslinked form of hyaluronic acid.

US patent 5 143 724 teaches the use of viscoelastic gel slurries of high biocompatibility. The patent relates to materials based on hyaluronic acid or s.c. hylans with very low cell interaction which is very useful in some applications but which has a limited value in tissue augmentation uses. The reason is because these materials will spread out in the tissue and loose it's augmenting property.

From the above it appears that the existing materials are clearly not ideal and the search for new improved materials for tissue augmentation continues with the aim to identify materials that are biocompatible, injectable through thin needles, non health threatening and has a residence time in tissues - short enough to disappear when their function is no longer desirable but long enough to be worth the effort to make the implantation.

The present invention addresses this aspect as well as that of versatility in designing an ideal composition for a specific tissue that needs to be augmented. In addition, these same compositions have proven to be very useful vehicles for the delivery of drugs.

SUMMARY OF THE INVENTION

The present invention provides for a composition for tissue augmentation that allows for a rich variety of polymers to be

injected through thin or long needles into desired position in the human or animal body. The implanted polymers can be composed to create different configurations in the tissue from very round ball-type forms to flat sheet formed implants. All this for the purpose of providing an optimal cosmetic result or therapeutic effect.

Although these conditions requiring tissue augmentation have been recognized for years and therapeutical and cosmetical solutions exist for the treatment thereof, the present invention provides novel compositions in the search for effective such treatment.

It is an object of the present invention, therefore, to provide novel compositions for tissue augmentation comprising a carrier gel having pseudoplastic (shear thinning) properties and one or more biocompatible, tissue augmenting substance(s).

It is yet another object of this invention to provide a composition for tissue augmentation in which the augmentation is partly by its ability to act as an in vivo cell specific stimulator of cell proliferation to develop specific types of tissues such as connective tissue, smooth muscles and more.

Another object of the invention is to provide a composition with the ability to evoke an immune response or even to develop specific glandular functions.

Yet another object of the present invention is to provide the above composition with one or more therapeutically active ingredient(s).

It is a further object of the present invention to provide novel methods for tissue augmentation of desired tissues of the human or animal body, giving a long lasting effect and no serious side effects.

These and further objects will become apparent by the below provided detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The biocompatible carrier gel of the composition according to the invention comprises a polymer dissolved in a suitable solution, such as physiological saline, as a matrix. The polymer is selected from the group consisting of glucose amine glucans, such as hyaluronic acid, hydroxy ethyl cellulose, carboxy methyl cellulose, xantahn gum, and alginates. Preferably, the matrix comprises 0.05-50% (w/w) of the composition. This carrier gel according to the invention has pseudoplastic properties, ie it has shear thinning properties.

The tissue augmenting substance of the composition according to the invention comprises water insoluble, biodegradable and biocompatible polymers. Examples of suitable polymers are collagen, starch, dextranomer, polylactide and copolymers thereof, poly-β-hydroxybutyrate and copolymers thereof.

The pseudoplastic properties of the carrier gel enables effective dispersion of the tissue augmenting substance therein. The dispersion can be formed at the time of injection or as a prefabricated formulation. In some cases it is also desirable for the composition to comprise one or more therapeutically active ingredient(s).

The active ingredient is selected from growth modulating factors, hormones, vaccines, cytokines, bacteriostatic or bacteriocidal agents or antiviral agents and other pharmacologically active compounds.

Furthermore the invention provides a method for tissue augmentation, comprising: injecting a composition described above into a desired site of the human or animal body for augmenting the tissue around said site.

This method also involves injecting the tissue augmentation material under fiberoptic guidance through long cannulas or catheters. In both cases, the pseudoplastic carrier is the most effective means to carry particulate polymers to a desired site, forming a right configuration and avoiding sedimentation or piling up the polymer in the injection system. The physical configuration is also an essential component in obtaining an optimal release rate from a sustained release preparation of active ingredient. In the case further augmentation is needed, the method is repeated after a certain time period from the first injection.

In a recent set of clinical investigations we also noticed an additional benefit of some of the augmenting substances. When analysing the tissue samples obtained at a second intervention of the patients, we noticed that depending on which type of augmenting microparticles used specific cells were recruited to the surface of the particles. Thus we also see a benefit of being able to augment the tissue by stimulating specific cells to proliferate and grow on the surface of the particles or to be recruited to a specific site of the body and there produce special materials such as collagen, growth stimulators, interferon and more. These techniques are partly known from the art of cell biology. This will be made much clearer in connection with the experimental part below.

The augmenting substance referred to in the present description is sometimes called microcarier having the equivalent meaning.

The invention will be disclosed in greater detail below in association with some non limiting Examples.

EXAMPLES

Example 1

1 gram of a fractionated size-defined medical grade dextranomer as augmenting substance was mixed with 100 mg of a high molecular weight hyaluronan fiber. To the mixture was added 25 ml of saline. The composition was dispersed into suitable syringes and heat sterilized for 20 minutes. The resulting slurry was then injected through a 30 gauge needle subcutaneously and the shape of the bolus was found to be very formable. After three to four weeks, histologic examination revealed a good integration of the dextran spheres with only a mild foreign body reaction. The pseudoplastic carrier had been reabsorbed.

Example 2

100 mg of an alginate (Pronova UP MVG) was dissolved in 5 grams of physiological saline solution to yield a highly viscous and pseudoplastic solution. To this solution was added 1 gram of a powder of poly-β-hydroxybutyrate as augmenting substance. The resulting slurry was injected under the skin of a nude mouse. A ball-shaped bolus was formed. The bolus was made harder by immediate follow-up of an injection of a 0.15 M calcium chloride solution.

Example 3

1 gram of collagen for use as augmenting substance was subjected to pepsin digestion and glutaraldehyde crosslinking and grinded to small 100 µm fragments. The slurry was made up to 25 ml of total volume by adding physiological saline. To the slurry was added 100 mg of high molecular weight hyaluronan fiber and 2.5 mg of lidocaine and adrenaline. The pseudoplastic fluid was transferred to syringes and injected subcutaneously into 5 healthy students. The composition was easy to inject and formed a distinct bolus. There was a short flash of pain upon injection but no bleeding. The augmented tissue was present for about 6 months (range 3-10). No adverse reaction was noticed.

Example 4

1 gram of cross-linked starch in the form of fibers was grinded to 100 µm fibers. The resulting aqeous slurry (25 ml) was heat sterilized and mixed with 100 mg of high molecular weight hyaluronan fibers. The reslutant pseudoplastic slurry was injected subcutaneously into nude mice. The augmentation lasted for more than 12 months as extrapolated from the 3 months evaluation. There was no sign of tissue reaction.

Example 5

1 gram of cross-linked starch in the form of microspheres (Spherex® Kabi-Pharmacia) was mixed with 20 ml of a 1 % hyaluronan solution (Hylartil® Pherrovet) and injected in the urether of a woman suffering from a mild form of incontinence. After six weeks, the incontinence returned to its pretreatment condition.

Example 6

The same woman as in Example 5 was subjected to a new treatment with an improved composition. Now, 1 gram of dextranomer (G 25 Ultrafine Sephadex® Kabi Pharmacia) was thoroughly washed until tested non-irritating followed by sterilization by heat. The microbeads were mixed with 20 ml of a 1 % solution of hyaluronan. Approximately 6 ml was injected in the urether under fiber optic guidance. After three weeks and additional 4 ml were injected as the previous treatment was considered inadequate.
At one year follow up, the woman was still continent and had no problem with the treatment.

Example 7

100 mg of a medical grade alginate (Pronova MGM) was dissolved in 20 ml of a balanced salt solution. To the viscous fluid was added 1 mg tranexam acid (a haemostatic agent) and 1 gram of dextranomer (as in Example 6). The resulting slurry was injected in the lip of a patient undergoing treatment for cosmetic surg ry. The 3 months result showed that the augmentation was

still present and the muscles of the lips were soft and homogeneous.

Example 8

In connection with the reconstruction of the root of a tooth it was noted that the epithelial lining of the attachment site was digested by bacterial enzymes. Surgery was performed and the area was cleaned and small holes were drilled in the bone adjacent to the reconstruction. A membrane was put to protect from overgrowth by the gingiva and under the membrane an augmenting microcarrier was injected with the following composition:
DEAE-Sephadex 50 mg/ml, size < 120 µm in isotonic buffer pH 7,4.
The blood was allowed to drain into the microcarrier suspension prior to closing of the wound.
At three months follow up a hard connective tissue was formed that later development into complete bone.
The fibroblasts known to attach to the microcarrier had been transformed to osteoblasts.

Example 9

Children suffering from vesicoureteral reflux can be cured by augmenting the tissue with the following composition:
Sephadex 50 mg/ml
Hyaluronic acid 12 mg/ml
pH 7,4
This composition was injected in the bladder wall at the orifice of the urether of children suffering from vesicouretheral reflux. A market stimulation of fibroblast proliferation and synthesis of collagen was noted already at two weeks after implantation. The result was that the reflux was completely stopped in 76% of the patients and improved in 10%.

Example 10

In an attempt to fill out wrinkles in the face of a woman the following composition was developed.
Dextranomer (Sephadex®) was suspended in a 0,5% solution of kitosan N-deacetylated at 85%. It was sucked dry by air and mixed at equal volymes with a 0,5% solution of a high molecular weight formulation of hyaluronic acid. The so formed suspension was injected intradermally just at the wrinkle bottom with a thin needle. The augmented portion of the skin showed at three months follow up a soft smoothening of the wrinkle with essentialy no tissue reaction. At biopsy the tissue speciment showed no sign of a foreign body reaction but a small ingrowth of collagen type II.

Example 11

A face with multiple scars from an earlier acne period was treated by subcutaneous injections of a formulation with the following composition. Sephadex® 50 mg/ml coated with kitosan 50% N-deacetylated. The coated Sephadex microspheres were suspended in a 0,5% heparin solution for 30 minutes at pH 8. A test with toulidine blue showed a marked colour of the dried microspheres indicating a high degree of surface coating of heparin. Inoculation of the mixture with EGF showed a high degree of binding to the microspheres. The resultant combination was injected as initially described.
The result showed a marked reduction of the acne scars at three months follow-up.

Example 12

An a-v port designed to allow quick and easy connection to the blood stream was surgically put in place. Previous trials had shown that the port was associated with coagulation complications and also by overgrowth of endothelial cells. To condition the

port the following modifications was made. At the contact sites of the vessel a multilayer of kitosan and heparin was applied. At the site of the movable parts a multilayer of kitosan and hyaluronic acid was applied. The results were that the overgrowth and coagulation problems were abolished for at least three months.

From the above it appears that the compositions and methods according to the present invention are suitable for therapeutical as well as cosmetical surgery for tissue augmenting purposes.

CLAIMS

1. A biocompatible composition for tissue augmentation, comprising a pseudoplastic polymer carrier in an amount of 0.05-50% (w/w) of the total composition; and one or more tissue augmenting substance(s) being water insoluble, biocompatible, and biodegradable.

2. A composition according to claim 1, wherein said pseudoplastic polymer carrier is selected from the group consisting of glucose amine glucans, such as hyaluronic acid, hydroxy ethyl cellulose, carboxy methyl cellulose, xantahn gum, and alginates.

3. A composition according to claim 1, wherein said tissue augmenting substance is a polymer and is selected from collagen, starch, dextranomer, polylactide and copolymers thereof, poly-β-hydroxybutyrate and copolymers thereof.

4. A composition according to any one of claims 1-3, wherein said tissue augmenting substances are surface modified to stimulate or inhibit the growth of specific cell types.

5. A composition according to any one of claims 1-4 also comprising one or more therapeutically active ingredient(s).

6. A composition according to claim 5, wherein said active ingredient(s) being in sustained release form.

7. A method for tissue augmentation, comprising:
injecting a composition of a pseudoplastic carrier comprising a tissue augmenting material and optionally an active ingredient into a desired site on the human or animal body for augmenting the tissue at and around said site.

8. A method according to claim 7, comprising injecting said composition under fiberoptic guidance.

9. A method according to claim 7 or 8, comprising repeating said injection after a certain time period.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00060

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5: A61K 47/38, A61K 47/36, A61L 27/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5: A61L, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, MEDLINE, WPI, WPIL, CLAIMS, CA SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,E	WO, A1, 9402184 (MEDINVENT), 3 February 1994 (03.02.94)	1-6
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X	EP, A2, 0466300 (BIOMATRIX INC.), 15 January 1992 (15.01.92), page 3, line 35 - page 7, line 54, the claims	1-6
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A	EP, A2, 0402031 (AMERICAN MEDICAL SYSTEMS, INC.), 12 December 1990 (12.12.90), claims	1-6
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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 July 1994	11 -07- 1994
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00060

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7-9
because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods (see PCT Rule 39(iv)

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/05/94

International application No.
PCT/SE 94/00060

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9402184	03/02/94	NONE	
EP-A2- 0466300	15/01/92	AU-B- 629467	01/10/92
		AU-A- 7405591	09/01/92
		CA-A- 2041074	10/01/92
		JP-A- 4261664	17/09/92
		US-A- 5143724	01/09/92
		US-A- 5246698	21/09/93
EP-A2- 0402031	12/12/90	CA-A- 2018448	09/12/90
		DE-D,T- 69005031	21/04/94
		JP-A- 3030771	08/02/91
		US-A- 5007940	16/04/91
		US-A- 5116387	26/05/92
		US-A- 5158573	27/10/92